

## Scl represses cardiomyogenesis in prospective hemogenic endothelium and endocardium.

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**Authors:** Ben Van Handel, Amelie Montel-Hagen, Rajkumar Sasidharan, Haruko Nakano, Roberto Ferrari, Cornelis J Boogerd, Johann Schredelseker, Yanling Wang, Sean Hunter, Tonis Org, Jian Zhou, Xinmin Li, Matteo Pellegrini, Jau-Nian Chen, Stuart H Orkin, Siavash K Kurdastani, Sylvia M Evans, Atsushi Nakano, Hanna K A Mikkola

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### Public Summary:

Endothelium in embryonic hematopoietic tissues generates hematopoietic stem/progenitor cells; however, it is unknown how its unique potential is specified. We show that transcription factor Scl/Tal1 is essential for both establishing the hematopoietic transcriptional program in hemogenic endothelium and preventing its misspecification to a cardiomyogenic fate. Scl(-/-) embryos activated a cardiac transcriptional program in yolk sac endothelium, leading to the emergence of CD31(+)Pdgralpha(+) cardiogenic precursors that generated spontaneously beating cardiomyocytes. Ectopic cardiogenesis was also observed in Scl(-/-) hearts, where the disorganized endocardium precociously differentiated into cardiomyocytes. Induction of mosaic deletion of Scl in Scl(f/f)Rosa26Cre-ER(T2) embryos revealed a cell-intrinsic, temporal requirement for Scl to prevent cardiomyogenesis from endothelium. Scl(-/-) endothelium also upregulated the expression of Wnt antagonists, which promoted rapid cardiomyocyte differentiation of ectopic cardiogenic cells. These results reveal unexpected plasticity in embryonic endothelium such that loss of a single master regulator can induce ectopic cardiomyogenesis from endothelial cells.

### Scientific Abstract:

Endothelium in embryonic hematopoietic tissues generates hematopoietic stem/progenitor cells; however, it is unknown how its unique potential is specified. We show that transcription factor Scl/Tal1 is essential for both establishing the hematopoietic transcriptional program in hemogenic endothelium and preventing its misspecification to a cardiomyogenic fate. Scl(-/-) embryos activated a cardiac transcriptional program in yolk sac endothelium, leading to the emergence of CD31(+)Pdgralpha(+) cardiogenic precursors that generated spontaneously beating cardiomyocytes. Ectopic cardiogenesis was also observed in Scl(-/-) hearts, where the disorganized endocardium precociously differentiated into cardiomyocytes. Induction of mosaic deletion of Scl in Scl(f/f)Rosa26Cre-ER(T2) embryos revealed a cell-intrinsic, temporal requirement for Scl to prevent cardiomyogenesis from endothelium. Scl(-/-) endothelium also upregulated the expression of Wnt antagonists, which promoted rapid cardiomyocyte differentiation of ectopic cardiogenic cells. These results reveal unexpected plasticity in embryonic endothelium such that loss of a single master regulator can induce ectopic cardiomyogenesis from endothelial cells.

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